



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P-INCI-X-04-0274		FOR FURTHER ACTION		See Form PCT/IPEA416
International application No. PCT/EP2004/008511		International filing date (day/month/year) 29.07.2004		Priority date (day/month/year) 30.07.2003
International Patent Classification (IPC) or national classification and IPC A61K31/4045, C07D209/08, C07D409/12, C07D513/04, A61K31/429, A61P3/04				
Applicant LABORATORIOS DEL DR. ESTEVE S.A. et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 28.02.2005		Date of completion of this report 30.06.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Telephone No. +49 89 2399- 		

INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITYInternational application No.
PCT/EP2004/008511

Box No. 1 Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-92 as originally filed

Claims, Numbers

1-73 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
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International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-73
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-73
Industrial applicability (IA)	Yes: Claims	1-73
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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International application No.

PCT/EP2004/008511**Re Item V****Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Reference is made to the following documents:**

- D1: WO 03/042175 A (ESTEVE LABOR DR) 22 May 2003 (2003-05-22)
- D2: EP-A-0 815 861 (HOFFMANN LA ROCHE) 7 January 1998 (1998-01-07)
- D3: WO 02/060871 A (FLAUGH MICHAEL EDWARD ; GILLIG JAMES RONALD (US); HEINZ LAWRENCE JOSEP) 8 August 2002 (2002-08-08)
- D4: US-A-3 472 870 (GOULD BARBARA E ET AL) 14 October 1969 (1969-10-14)
- D5: EP-A-0 471 609 (SANOFI SA ; SANOFI PHARMA N V SA (BE)) 19 February 1992 (1992-02-19)

2. Novelty (Article 33(1) and (2)PCT)

The present application discloses compounds of formula (Ia-b) (see present Claims 1, 9), which are useful as 5-HT-6 modulators.

The present compounds(see Claims 1 and 9) differ from the D1 compounds on the account of the present R1 substituent, from the D2 compounds on the account of position 5 of substitution with sulfonamide moiety on the indole ring (instead of the 4-th position for the D2 compounds), from the D3 compounds on the account of the sulfonamide moiety (see Claim 1), from the D4 and D5 compounds on the account of the A substituent of the sulfonamide function (which in the present case should contain a (hetero)aromatic ring and for the D4-D5 compounds is an alkyl or alkenyl moiety). Consequently, the novelty of the present subject-matter is acknowledged.

3. Inventive step (Article 33(1) and 33(3) PCT)

The present application discloses 5-sulfonamidoindoles which are substituted on position 1 of the indole with an amino moiety or with a (hetero) cycloaliphatic ring useful as 5-HT-6 modulators.

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D1 , which is regarded as being the closest prior art, discloses 5-HT-6 modulators which are also sulfonamide indoles. The main difference between the present compounds and the compounds disclosed by D1 is the position of substitution with the $-(CH_2)_n-R_1$ moiety on the indole ring which is not in the first position (as for the present case) but in the 3-rd position of the indole ring for the D1 compounds (see present Claim 1 and the Claim 1 of D1).

The problem underlying the present invention cannot be regarded in providing further sulfonamide indoles useful to treat diseases modulated through the 5-HT-6 receptor, for the following reasons:

D3 discloses indol-5-yl esters which are 5-HT6 antagonists and are substituted in the position 1 of the indole ring with the same moieties as in the present case (see e.g. examples 23, 28, 67 of D3 and the present Claim 1).

The present general structures (Ia) differ from the compounds disclosed by D1 only through the position of substitution with $-(CH_2)_n-R_1$ moiety on the indole ring (the 1-st position in the present case and the 3-rd in D1 case). D3 teaches that compounds substituted in position 1 with a cycloaliphatic ring (see e.g. examples 23, 28, 67 of D3) are useful as 5-HT-6 modulators.

Having regard that the present compounds differ from D1 compounds only through the position of the substitution with R_1 substituent on the indole ring, and that the D3 discloses 5-HT-6 ligands which bear on the nitrogen of the indole ring the same substituents as in the present case, the skilled person would have combined the teaching of D3 with the teaching of D1 in order to solve the above-mentioned problem.

The problem underlying the present application should thus be seen in providing of sulfonamide indole derivatives with unexpected or surprising effects compared to those of the closest prior art. An inventive step cannot be recognized as it is not yet shown by appropriate information, e.g. in form of experimental data, that substantially all the claimed compounds have an unexpected property or improved activity over the structurally closest prior art compounds (D1), which is attributable to the distinguishing feature of the invention.